Portal vein thrombosis can aggravate esophageal variceal bleeding after endoscopic variceal ligation

Dejian Li, Xufei Qi, Chao Lu, Chaohui Yu

Department of Gastroenterology, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China

Received July 28, 2017; Accepted November 21, 2017; Epub February 15, 2018; Published February 28, 2018

Abstract: Background: We aimed to evaluate whether portal vein thrombosis (PVT) and other factors influence esophageal variceal bleeding (EVB) after endoscopic variceal ligation (EVL) for liver cirrhosis patients. Methods: We retrospectively enrolled 255 patients with EVL in our hospital and parameters of age, gender, blood platelet, albumin, total bilirubin (TBil), D-dimer, activated partial thromboplastin time (APTT), prothrombin time (PT), Child-Pugh classification, portal vein thrombosis (PVT) and splenectomy were collected. Results: EVB patients had higher PVT diagnosed rate than non-EVB patients \( (P=0.009) \) and the rate of EVB had an increasing trend with the severity of ascites \( (P=0.034) \). On multivariate analysis, we still found PVT and ascites obviously affected incidence rate of EVB \((P=0.026, P=0.027, \text{respectively})\). Conclusion: PVT and ascites per se appeared to be the cause of EVB subsequent to EVL. If detected, anticoagulation or treatments refer to PVT and ascites needed to conducted in order to reduce the incidence of EVB after EVL.

Keywords: Portal vein thrombosis, esophageal variceal bleeding, endoscopic variceal ligation

Introduction

Liver cirrhosis is an increasing cause of morbidity and mortality, responsible for more than 1 million deaths annually [1]. Portal hypertension, esophageal varices and ascites are main complications of cirrhosis. Bleeding of esophageal varices is one of the most dreaded complications of portal hypertension since, in spite of all the achievements of the last decades, it is still associated with high mortality rates [2]. Therefore, prophylaxis of variceal hemorrhage, either to prevent first bleeding in patients with severe varices or to prevent rebleeding is very important [3, 4]. Endoscopic variceal ligation (EVL) can enhance the control of bleeding of esophageal varices or rebleeding in patients with liver cirrhosis or extrahepatic portal vein obstruction (EHPVO) [5, 6].

However, before EVL, we must evaluate the general conditions. Child classification, blood platelets count, infection may all affect the success rate of EVL. Dell’Era et al. also reported that portal vein thrombosis (PVT) per se appeared to be the cause of a longer time to achieve eradication of varices [7]. Therefore, portal vein thrombosis may also an important factor for EVL.

In our study, we aimed to assess whether portal vein thrombosis can influence the bleeding after EVL for liver cirrhosis patients. Secondary end-points were the relationship between portal vein thrombosis and splenectomy.

Materials and methods

Study cohort

We retrospectively enrolled 255 liver cirrhosis patients with EVL from January 1, 2011 to January 20, 2017 in the First Affiliated Hospital, College of Medicine, Zhejiang University. Etiologies of cirrhosis of our study were mostly hepatitis B virus infection, and also including alcohol and schistosome. Patients were included in the study according to the following crite-
PVT aggravate EVB after EVL

Table 1. Baseline characteristics of included patients

<table>
<thead>
<tr>
<th></th>
<th>EVB patients (11)</th>
<th>Non-EVB patients (244)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>53.09±9.36</td>
<td>53.59±10.27</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>9</td>
<td>190</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>PVT</td>
<td>7</td>
<td>66</td>
<td>=0.009</td>
</tr>
<tr>
<td>Splenectomy</td>
<td>4</td>
<td>64</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>APTT</td>
<td>34.21±8.16</td>
<td>36.05±9.3</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>PT</td>
<td>13.77±1.5</td>
<td>13.76±1.76</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>PLT</td>
<td>149.55±103.62</td>
<td>113.14±92.31</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Albumin</td>
<td>36.55±4.86</td>
<td>36.26±4.96</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>TBil</td>
<td>24.82±13.74</td>
<td>19.3±12.63</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>D-dimer</td>
<td>2667.45±2029.25</td>
<td>1339.75±1874.93</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Ascites</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>3</td>
<td>232</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Moderate</td>
<td>6</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Child-Pugh</td>
<td>6.73±1.42</td>
<td>6.2±1.28</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

EVB: esophageal variceal bleeding; PVT: portal vein thrombosis.

Experimental protocol was approved by the Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University.

Endoscopic band ligation

All band ligations were strict accordance with the relevant operations and specification drawn up by The Chinese society for digestive endoscopy in 2000. We used Olympus XQ240, 260 electronic gastroscope and six-band device, seven-band device by Wilson-Cook Corporation. Each of esophageal varices was choose segmented band ligation from bottom to top.

Data abstraction

In our study, which factors really influencing EVB was the main outcome which we wanted to know. Chi-square test was used to compare categorical variables. In addition, pair-wise comparison among multi-categorical variable groups was performed using Chi-square test combined with Bonferroni correction (P<0.05/n) [8]. Multivariate analysis was performed using logistic regression and coefficients of variables for multivariate model were estimated. The statistical significance was defined as P<0.05. We used SPSS 21.0 (IBM, Chicago, IL) to perform the statistical analysis. In addition, another associated data was calculated and plotted using GraphPad Prism 5 (Graph Pad, San Diego, CA).

ria: (1) diagnostic criteria of cirrhosis was histology or unequivocal clinical, laboratory and image findings; (2) in our study, PVT was diagnosed by CT liver angiography and the location of PVT was main portal vein; (3) EVL was firstly conducted without previous treatment such as esophageal variciform sclerotherapy (EVS) or transjugular intrahepatic portosystemic shunt (TIPS); (4) at least two weeks of hospitalized follow-up after EVL; (5) written informed consent to the procedures; (6) older than the age of 18; (7) both primary prophylaxis patients and acute variceal bleeding patients. And patients were excluded according to the following criteria: (1) patients with other chronic diseases such as coronary heart disease, chronic obstructive pulmonary disease, diabetes mellitus, cancer and so on; (2) lacking of data which I wanted; (3) EVL was not the first treatment for esophageal varices; (4) patients with the presence of hepatocellular carcinoma and PVT due to neoplastic vascular invasion explicit; (5) repeated EVL treatment after the first time. Finally, 866 patients were excluded because of above reasons.

PVT was diagnosed by CT liver angiography with filling defect of portal vein.

In our study, informed consent was signed from all subjects and their privacy was respected.
PVT aggravate EVB after EVL

Results

Baseline characteristics

The baseline characteristics were shown in Table 1. The mean age of the enrolled patients was 53.57 years old (53.57±10.22). Among them, man occupied 78.04% (199/255), while woman was 21.96% (56/255). Finally, 11 patients had EVB including 1 patient died and 244 had non-EVB. The hematological parameters were also listed in Table 1.

Univariate analysis between EVB and non-EVB patients

We found that EVB patients had higher PVT diagnosed rate than non-EVB patients (63.64% vs. 27.05%, \(P=0.009\)) (Figure 1A). Other results were listed in Table 1. In addition, EVB patients had higher D-dimer (\(P=0.023\)) and higher radio of moderate and severe ascites (\(P<0.001\)) than non-EVB patients. Mild ascites had 1.96% (3/153) EVB, moderate ascites had 6.82% (6/70) EVB and severe ascites had 14.29% (2/14) EVB. There were statistical differences between each of them (\(P=0.034\)) (Figure 1B).

In our study, Child-Pugh classification did not affect the EVB (\(P>0.05\)). We then divided Child-Pugh classification into grade A, grade B and grade C. Child A had 3.57% (6/168) EVB, Child B had 5.95% (5/84) EVB, while Child C had no EVB (0/3) (Figure 2A). There were also no statistical differences between each of them (\(P>0.05\)). Child A and B had no differences, either (\(P>0.05\)).

Moreover, we found that PVT was obviously related to splenectomy (coefficient =2.629, \(P<0.001\)). There was no difference of EVB rate between splenectomy (5.88%) and no splenectomy (3.74%) patients (\(P>0.05\)) (Figure 2B).
PVT aggravate EVB after EVL

On multivariate analysis, we still found PVT obviously affected incidence rate of EVB (coefficient = 1.449, \( P = 0.026 \)) (Table 2). It indicated that PVT still is an important influence for EVB after EVL. In addition, ascites was another factor affecting EVB (coefficient = -1.029, \( P = 0.027 \)) (Table 2). The more severe ascites, the higher incidence of EVB.

**Table 2. Multivariate analysis between EVB and non-EVB patients**

<table>
<thead>
<tr>
<th>Variable</th>
<th>( \beta )</th>
<th>S.E.</th>
<th>( \chi^2 )</th>
<th>P</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVT</td>
<td>1.449</td>
<td>0.652</td>
<td>4.941</td>
<td>0.026</td>
<td>4.261</td>
</tr>
<tr>
<td>Ascites</td>
<td>-1.029</td>
<td>0.465</td>
<td>4.894</td>
<td>0.027</td>
<td>0.357</td>
</tr>
</tbody>
</table>

PVT: portal vein thrombosis.

**Discussion**

EVL is one of the therapeutic options proposed for patients with esophageal varices at high risk of bleeding or rebleeding. Various factors may influence the curative effect of EVL. In our study, we found PVT and ascites can improve the hemorrhage after EVL. Moreover, there was positive correlation between PVT and splenectomy.

We know that liver cirrhosis is often accompanied by hypersplenism, which results in the decrease of akaryocyte, leukocyte and platelet. Splenectomy is one of the treatment means for portal hypertension of liver cirrhosis. The reported incidence of PVT subsequent to splenectomy differs markedly, ranging from 0.36% [9] to 80% [10], while it was 69.12% in our study. The detailed mechanism for the formation of PVT after splenectomy remained unclear. It is hypothesized to be associated with local hypercoagulability occurring in the portal vein system after surgery, which may be attributed to soaring count and augmented aggregation competence of platelets post-surgery [11]. In addition, local hemodynamic changes of portal vein and operative, which may lead to serious damage of vascular endothelial cells and trigger the coagulation system may be other important reasons for the formation of PVT [12, 13]. Zhang et al reported that early prophylactic anticoagulation may reduce the incidence of PVT following splenectomy [14].

Incidence of PVT in our study was 28.63% and PVT was higher in EVB patients after EVL. Further increase of portal vein by PVT may improve the risk of bleeding after EVL. In addition, local hypercoagulability may also aggravate the esophageal and gastric varices. Qi et al reported a systemic review mentioned that the presence of PVT should be positively associated with the risk of portal hypertension-related bleeding in liver cirrhosis, while there was no coincident result [15]. Dell’Era et al. reported that PVT per se appeared to be the cause of a longer time to achieve eradication of varices but, once eradication was achieved, it did not influence their recurrence [7]. Lee et al. found that ascites and PVT were no significant influence on recurrent hemorrhage in cirrhotic patients [16]. The pathogenesis of PVT includes both “systemic factors” including coagulation abnormalities or presence of antiphospholipid antibodies [17] and “local factors”, as peri-portal lymphangitis and fibrosis that lead to alteration of liver cytoarchitecture with consequent flow reduction and endothelial activation [18-20]. Leonardi F et al. indicated that the use of anticoagulants both as treatment or prophylaxis is safe, reduces the rate of PVT and decompensation, and improves survival [21].

In our study, ascites was positively related to EVB, while there was no difference of Child-Pugh classification. Therefore, the severity of ascites may be resulted from PVT to affect EVB subsequent to EVL. Moreover, abdominal bacterial infection may be the reason of ascites and reducing the rebleeding after EVL. Yang et al. reported that bacterial infection and end-stage liver cirrhosis (Child C) were the independent risk factors for early bleeding after EVL [22].

Given the retrospective nature of this study, some limitations should be taken into account although we got some significant results. First, inclusion bias cannot be excluded such as the severity difference of esophageal varices (EV). Different classification of EV would influence the prognosis of treatment. In addition, although CT liver angiography was sensitive to PVT, for small thrombus, there was the possibility of misdiagnosis. Patients understanding of the hospital would also change the selection of therapeutic schedule. Second, the low number of patients included may not provide enough
PVT aggravate EVB after EVL

evidence to our results. And we selected 14-day follow-up as observation time due to hospital stays. We were not explicit whether 20-day, 30-day or longer time would appear events of EVB.

In conclusion, portal vein thrombosis and ascites per se appeared to be the cause of EVB subsequent to EVL. The dreadful adverse event of bleeding from early band detachment was sporadic. Since patients with cirrhosis with PVT or ascites, anticoagulation or treatments refer to ascites needed to conduct in order to reduce the incidence of EVB after EVL. Finally, we need more multi-center perspective studies to support our results.

Acknowledgements

Informed consent was obtained from all patients for being included in the study.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Chaohui Yu, Department of Gastroenterology, The First Affiliated Hospital, College of Medicine, Zhejiang University, 79 Qingchun Road, Hangzhou 310003, China. Tel: +86-571-87236532; E-mail: luhaha213@163.com

References

PVT aggravate EVB after EVL


